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PLASMA VERY LONG-CHAIN N-3 POLYUNSATURATED FATTY ACIDS AND AGE-RELATED HEARING LOSS IN OLDER ADULTS

C. DULLEMEIJER, P. VERHOEF, I.A. BROUWER, F.J. KOK, R.-J.M. BRUMMER, J. DURGA

Division of Human Nutrition, Wageningen University, the Netherlands (CD, PV, IAB, FJK, JD); Top Institute Food and Nutrition, Wageningen, the Netherlands (CD, PV, IAB, RJMB, JD); Institute of Health Sciences, VU University Amsterdam, the Netherlands (IAB). Corresponding author: Carla Dullemeijer, Division of Human Nutrition, Wageningen University, P.O. Box 8129, 6700 EV Wageningen, the Netherlands, e-mail: Carla.Dullemeijer@wur.nl.

Abstract: *Objectives:* Age-related hearing loss is a common social and health problem in the older adult population. Up until now, very little scientific attention has been given to the potential role of fatty acids in age-related hearing loss. In this study we investigated whether plasma very long-chain n-3 polyunsaturated fatty acids (PUFAs) are associated with age-related hearing loss over three years. *Design:* Cross-sectional and 3-year longitudinal analyses. *Setting:* Wageningen, the Netherlands. *Participants:* 720 men and postmenopausal women (50-70 years of age) without middle ear dysfunction or unilateral hearing loss. *Measurements:* Fatty acid proportions were measured in plasma cholesteryl esters. Hearing thresholds (in decibels, dB) at baseline and after three years were measured with pure-tone audiometry. Hearing loss was calculated as the increase in mean hearing thresholds in the low (0.5-kHz, 1-kHz, and 2-kHz) and high (4-kHz, 6-kHz, and 8-kHz) frequencies over three years. *Results:* Subjects in the highest quartile of plasma very long-chain n-3 PUFA had less hearing loss in the low frequencies over three years than subjects in the lowest quartile ($p<0.01$, ANCOVA, difference in mean adjusted hearing thresholds= -1.2 dB). There were no significant differences between the quartiles of plasma very long-chain n-3 PUFA in hearing loss in the high frequencies ($p=0.49$, ANCOVA). These associations are adjusted for baseline mean hearing thresholds, age, sex, level of education and alcohol consumption. *Conclusion:* This study is the first to show an inverse association between plasma very long-chain n-3 PUFAs and age-related hearing loss. These results are encouraging, but require confirmation from future studies.

Key words: n-3 fatty acids, omega-3 fatty acids, n-3 PUFA, hearing, older adults.

Introduction

Age-related hearing loss is attributed to age-related degeneration of the cochlea as well as other physiologic, environmental, and pathological processes that occur during the lifespan (1). It initially affects hearing sensitivity in the high-frequencies, affecting communication in noisy situations. Once the loss extends to the lower frequencies (2-4 kHz range), important for understanding the voiceless consonants, speech understanding in any situation is affected (1). Age-related hearing loss is a common chronic condition, affecting 30-35% of the people aged 65-75 years and 40-50% of the people over 75 years (2).

The relationship between hearing loss and nutritional status is a relatively new area of investigation (2). The hypothesis that nutrition may play a role in age-related hearing loss is based on evidence from two converging research areas: research showing that hearing loss is related to vascular disease (3-6), and research showing that vascular systems rely on certain nutrients for optimal structure and function (2). Very long-chain n-3 polyunsaturated fatty acids (n-3 PUFA), as present in fish and fish oil, are suggested to protect against vascular diseases (7). Since the cochlea is highly vascularised, it has been suggested that age-related hearing loss may be caused by a decrease in the blood supply to the cochlea (5).

Very little scientific attention has been given to the potential role of fatty acids in age-related hearing loss. A study in two psychiatric hospitals in Finland showed that adults who consumed a low fat diet for a period of five years had better hearing levels throughout the entire audiometric range than adults who consumed a diet high in saturated fatty acids (8). However, there are currently no published studies that have investigated the relationship between very long-chain n-3 PUFAs and age-related hearing loss. Therefore, the present study assesses whether plasma very long-chain n-3 PUFAs are associated with age-related hearing loss over a period of three years in a population of Dutch older adults.

Subjects and methods

Subjects

We used data from participants of the FACIT study, a randomized controlled trial investigating the effect of folic acid supplementation on hearing, carotid intima-media thickness and cognitive performance (9). In this study, 819 men and postmenopausal women aged 50-70 years were randomly assigned to either folic acid (n=406) or placebo (n=413) treatment for a period of 3 years. Participants were recruited by using municipal and local blood bank registries from the Gelderland province in the Netherlands. Major exclusion criteria were plasma total homocysteine levels <13 μmol/L and >26 μmol/L, serum vitamin B12 levels <200pmol/L, renal or thyroid diseases, and current use of B-vitamin supplements. The baseline measurements, which included measurements of

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hearing, were conducted between 2000 and 2001. The original study on which the present article is based was approved by the Medical Ethics Committee of Wageningen University, the Netherlands. All study participants provided written informed consent.

In our analyses, subjects with middle ear dysfunction (defined as air-bone gap ≥15 dB on the audiogram of either ear) or unilateral hearing loss (≥20 dB difference in mean pure-tone hearing thresholds for 0.5 kHz, 1 kHz, and 2 kHz between the right and left ear) were excluded (n=91), as these hearing problems are unlikely due to age-related hearing loss. In addition, we excluded eight participants from whom insufficient amounts of blood could be obtained or who did not give permission for the fatty acid analyses, resulting in a total of 720 participants.

Audiometric measurements

Excessive cerumen, if present, was removed from the participants' ears prior to the audiometric measurements. The pure tone audiometric assessments were performed in an acoustical booth (Audiofon G, Audiovox, Hauppauge, New York), which muted sounds up to 42 dB and was placed in a quiet, isolated, carpeted room next to the college library. Participants were measured in seated position using an audiometer (Madsen Voyager 522, Madsen Electronics, Taastrup, Denmark), circum-aural earphones and a handheld response button system. We calibrated the audiometer according to the International Organization of Standardization standard 389 and we performed the audiometric testing by using a variation of the Hughson and Westlake method as described earlier (9). Our outcomes measures are the mean pure-tone air conduction hearing thresholds in the low (0.5-kHz, 1-kHz, and 2-kHz) and high (4-kHz, 6-kHz, and 8-kHz) frequencies.

To enable exclusion of participants with possible middle ear dysfunction at the start of the study, we measured bone conduction hearing thresholds at 0.5 kHz, 1 kHz, 2 kHz, and 4 kHz by using contra-lateral masking. To enable exclusion of participants with unilateral hearing loss at the start of the study, we used contra-lateral masking when the difference in air conduction hearing threshold between the right and left ear was 50 dB or more. Subjects with a difference of 20 dB or more in mean air conduction hearing thresholds after contra-lateral masking between the right and left ear were excluded from the analyses.

Plasma n-3 PUFA proportions

Venous blood was collected after an overnight fast in one 10-ml Vacutainer tube containing ethylene diamine tetra-acetic acid (EDTA). The obtained plasma was stored within 2 hours at -80°C until analysis. Fatty acids in plasma cholesteryl esters were determined as described previously (10). We calculated plasma very-long chain n-3 PUFAs by adding up the levels of eicosapentaenoic acid (EPA), docosapentaenoic acid (n-3 DPA), and docosahexaenoic acid (DHA).

Other measurements

At baseline, participants completed a questionnaire on general demographic variables and medical history. Height and weight were measured to calculate body mass index (kg/m2). Level of education was divided into three groups according to the highest level attained: primary education, junior vocational training and senior vocational or academic training. Blood pressure was measured using an automated meter (Dinamap Compact Pro 100, General Electric, Waukesha, Wisconsin) and we took the mean of eight measurements. Serum total cholesterol, LDL-cholesterol and HDL-cholesterol were determined on a Hitachi® 747 analyzer (Roche Diagnostics, Mannheim, Germany). Physical activity was estimated using the Physical Activity Scale for the Elderly (11).

Statistical analyses

Subjects were grouped according to quartiles of plasma very long-chain n-3 PUFA proportions. Equality of variances was tested using Levene's tests. Baseline characteristics of subjects in the different quartiles were compared with chi-square tests, one-way analysis of variance (normally distributed variables), or Kruskal-Wallis tests (non-normally distributed variables). Analysis of covariance (ANCOVA) was used to evaluate the association between quartiles of plasma very long-chain n-3 PUFAs and mean hearing thresholds in the low (0.5-kHz, 1-kHz, and 2-kHz) and high (4-kHz, 6-kHz, and 8-kHz) frequencies. Because we excluded participants with unilateral hearing loss, we averaged the hearing thresholds from both ears in our outcome measures. When significant F-tests were obtained, Tukey's honest significant difference tests were applied for the post hoc comparison. We evaluated age, sex, level of education, smoking, alcohol consumption and erythrocyte folate concentrations as potential confounders. To investigate whether the folic acid treatment was an effect modifier in the longitudinal analyses, we performed stratified analysis by intervention group. Statistical significance for all analyses was defined as $p<0.05$. The data analyses were performed with the Statistical Analysis System (SAS version 9.1.3; SAS Institute Inc, Cary, NC).

Results

The mean age of our participants at baseline was 60 years and 72% of our study population was male. When grouped according to quartiles of plasma very long-chain n-3 PUFA, there were no differences between the four groups in age, sex, level of education, body mass index, smoking habits, physical activity, blood pressure and blood parameters (Table 1). Alcohol consumption was higher in the highest quartile of very long-chain n-3 PUFA than in the lowest quartile. The proportions of individual fatty acids in plasma cholesteryl esters according to quartiles of plasma very long-chain n-3 PUFAs are shown in Table 2.

Table 1
Baseline characteristics of participants according to quartiles of plasma very long-chain n-3 PUFAs[a]

Characteristics	Quartile 1 (n=180)	Quartile 2 (n=180)	Quartile 3 (n=180)	Quartile 4 (n=180)
Age (y)	60.0 ± 6.0	59.8 ± 5.6	60.1 ± 5.4	60.5 ± 5.4
Gender (M/F)	140 / 40	133 / 47	122 / 58	122 / 58
Level of education (low/middle/high)[b]	47 / 62 / 71	44 / 66 / 70	39 / 74 / 67	34 / 68 / 78
BMI (kg/m^2)	26.1 ± 3.5	26.7 ± 3.3	26.8 ± 3.8	26.8 ± 3.8
Smoking (never / former / current)	56 / 89 / 35	55 / 94 / 31	50 / 87 / 43	40 / 107 / 33
Alcohol consumption (g/day)	8.6 (1.7 – 15.7)	13.6 (4.5 – 22.3)	13.3 (5.2 – 26.5)	17.2 (7.6 – 27.5)
Physical Activity (PASE score)	150 ± 71	163 ± 68	155 ± 73	145 ± 61
Self-reported hearing problems	16	21	17	19
Serum total cholesterol (mmol/L)	5.64 ± 0.99	5.76 ± 1.11	5.97 ± 1.02	5.91 ± 1.17
Serum LDL cholesterol (mmol/L)[c]	3.87 ± 0.87	3.96 ± 0.97	4.13 ± 0.91	4.07 ± 1.02
Serum HDL cholesterol (mmol/L)	1.23 ± 0.32	1.21 ± 0.34	1.23 ± 0.35	1.28 ± 0.40
Systolic blood pressure (mm Hg)[d]	132 ± 16	132 ± 16	134 ± 17	133 ± 15
Diastolic blood pressure (mm Hg)[d]	77 ± 8	77 ± 9	77 ± 8	77 ± 8

Values are means ± SD, medians (interquartile range) or n. a. Plasma very long-chain n-3 PUFA quartiles 1: <1.18%; 2: 1.18-1.51%; 3: 1.52-2.04%; 4: >2.04%. b. Low=primary education; Middle=junior vocational training; High= senior vocational or academic training. c. Data available for 718 participants. d. Data available for 716 participants.

Table 2
Fatty acid contents (% of total fatty acids) in plasma cholesteryl esters according to quartiles of plasma very long-chain n-3 PUFAs[a]

Fatty acids	Quartile 1 (n=180)	Quartile 2 (n=180)	Quartile 3 (n=180)	Quartile 4 (n=180)
Saturated fatty acids, total	12.2 ± 1.1	12.9 ± 1.2	13.0 ± 1.1	13.2 ± 1.0
Palmitic acid, 16:0	10.5 ± 0.8	11.0 ± 0.9	11.1 ± 0.9	11.3 ± 0.8
Stearic acid, 18:0	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2
N-9 mono-unsaturated fatty acids, total	16.3 ± 2.2	17.0 ± 2.3	17.4 ± 2.3	17.8 ± 2.2
Oleic acid, 18:1n-9	16.3 ± 2.2	17.0 ± 2.3	17.4 ± 2.3	17.8 ± 2.2
N-6 polyunsaturated fatty acids, total	64.8 ± 3.9	62.4 ± 4.1	61.2 ± 4.3	59.3 ± 4.1
Linoleic acid, 18:2n-6	57.2 ± 4.2	53.8 ± 4.7	52.6 ± 4.9	50.9 ± 4.5
Arachidonic acid, 20:4n-6	6.0 ± 1.5	6.9 ± 1.4	6.9 ± 1.4	6.8 ± 1.3
N-3 polyunsaturated fatty acids, total	1.6 ± 0.2	2.0 ± 0.2	2.3 ± 0.2	3.4 ± 0.9
-Linolenic acid, 18:3n-3	0.6 ± 0.2	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1
Eicosapentaenoic acid, 20:5n-3	0.6 ± 0.1	0.8 ± 0.1	1.1 ± 0.2	2.0 ± 0.8
Docosapentaenoic acid, 22:5n-3	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Docosahexaenoic acid, 22:6n-3	0.4 ± 0.1	0.5 ± 0.1	0.6 ± 0.1	0.8 ± 0.2

Values are means (SD). a. Plasma very long-chain n-3 PUFA quartiles 1: <1.18%; 2: 1.18-1.51%; 3: 1.52-2.04%; 4: >2.04%.

Hearing loss over three years (longitudinal results)

We were able to analyze the data of 705 of the 720 participants in our longitudinal analyses. Fifteen participants did not provide hearing data after three years, because they died during the follow-up (n=11), or were lost to follow-up (n=4).

The mean increase in all participants in hearing threshold over three years was 1.4 dB (95% CI: 1.1 to 1.7) for the low frequencies and 4.8 dB (95% CI: 4.4 to 5.2) for the high frequencies. Subjects in the highest quartile of very long-chain n-3 PUFA had less hearing loss in the low frequencies over three years than subjects in the lowest quartile (Table 3, p<0.01, ANCOVA). The difference in the adjusted mean hearing thresholds in the low frequencies between the highest and lowest quartile was -1.2 dB (95%CI: -2.2 to -0.1). There were no significant differences between the quartiles of plasma very long-chain n-3 PUFA in mean hearing thresholds in the high frequencies after three years (p=0.49, ANCOVA). These longitudinal associations were adjusted for baseline mean hearing threshold values, age, sex, level of education and alcohol consumption.

Because we previously showed that the folic acid treatment slowed down the decline in mean hearing threshold in the low frequencies (9), we performed the longitudinal analyses also separately for the placebo group and the folic acid group. When considering the longitudinal analyses separately for the placebo and the folic acid group, it appeared that higher proportions of plasma very long-chain n-3 PUFA were still associated with less hearing loss over three years in the low frequencies in the placebo group. The difference in mean hearing threshold in the low frequencies between the highest and lowest quartile was -1.8 dB (95%CI -3.2 to -0.3). In the folic acid group, however, the association was not statistically significant.

Table 3
Hearing thresholds in the low and high frequencies after 3 years according to quartiles of plasma very long-chain n-3 PUFAs[a]

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-value[b]
All participants					
Sample size, n	176	177	175	177	
Hearing threshold on low frequencies, dB	15.7 (15.1; 16.2)[c]	15.4 (14.8; 15.9)[cd]	14.6 (14.1; 15.2)[d]	14.5 (14.0; 15.1)[d]	<0.01
Hearing threshold on high frequencies, dB	42.4 (41.5; 43.3)	42.6 (41.8; 43.5)	41.7 (40.8; 42.6)	42.2 (41.3; 43.1)	0.49
Placebo group only					
Sample size, n	91	90	90	91	
Hearing threshold on low frequencies, dB	16.1 (15.3; 16.8)[c]	15.5 (14.7; 16.2)[cd]	14.8 (14.1; 15.5)[cd]	14.3 (13.6; 15.1)[d]	<0.01
Hearing threshold on high frequencies, dB	42.5 (41.3; 43.8)	43.4 (42.2; 44.6)	42.5 (41.3; 43.7)	42.3 (41.1; 43.5)	0.58
Folic acid group only					
Sample size, n	85	87	86	85	
Hearing threshold on low frequencies, dB	15.1 (14.3; 15.9)	15.4 (14.7; 16.2)	14.4 (13.6; 15.2)	14.7 (13.9; 15.5)	0.31
Hearing threshold on high frequencies, dB	42.0 (40.8; 43.3)	42.1 (40.8; 43.4)	40.9 (39.6; 42.2)	42.0 (40.7; 43.3)	0.51

Results are adjusted means (95% CI); dB=decibel. a. Plasma very long-chain n-3 PUFA quartiles 1: <1.18%; 2: 1.18-1.51%; 3: 1.52-2.04%; 4: >2.04% (all participants). b. ANCOVA adjusted for baseline mean hearing threshold, age, sex, level of education and alcohol consumption. Post-hoc comparison by Tukey's Honest Significant Differences test (means in a row with different superscript letters are significantly different).

Because the study by Rosen et al. (8) reported worse hearing thresholds in persons on a saturated fat diet compared with persons on a low fat diet, we also evaluated the associations between plasma saturated fatty acids and mean hearing thresholds (data not shown). However, there were no significant differences between the quartiles of plasma saturated fatty acids in mean hearing thresholds in the low or high frequencies after three years (p=0.46 and p=0.29 for ANCOVA, respectively).

Hearing thresholds (cross-sectional results)

There were no significant differences between the four quartiles of plasma very long-chain n-3 PUFA in the mean hearing threshold at baseline in the low frequencies (Q1 (Quartile 1): 13.5 (95%CI: 12.1 to 14.8); Q2: 14.6 (95%CI: 13.3 to 15.9); Q3: 13.8 (95%CI: 12.5 to 15.1); Q4: 12.6 (95%CI: 11.3 to 13.9; p=0.21 for ANCOVA), after adjustments for age, sex, and education level. In addition, no significant differences between the quartiles were found in the mean hearing threshold in the high frequencies (Q1: 36.9 (95%CI: 34.5 to 39.3); Q2: 38.1 (95%CI: 35.7 to 40.5); Q3: 39.5 (95%CI: 37.1 to 41.9); Q4: 35.4 (95%CI: 33.0 to 37.9); p=0.12 for ANCOVA), after adjustments for the same confounders.

Mean hearing thresholds in the low and high frequencies were not significantly different between quartiles of plasma saturated fatty acids (p=0.36 and p=0.54 for ANCOVA, respectively), although the results were in the expected direction. Mean hearing thresholds on the low and high frequencies tended to be higher for the highest quartile of saturated fatty acids, compared with the lowest quartile of saturated fatty acids (data not shown).

Discussion

The present study in older adults shows that people in the highest quartile of plasma very long-chain n-3 PUFAs had less hearing loss in the low frequencies over three years than people in the lowest quartile. Plasma very long-chain n-3 PUFAs appeared not to be associated with hearing loss in the high frequencies.

The hearing loss in our study population was likely to be age-related hearing loss of cochlear origin. By excluding participants with middle-ear dysfunction and unilateral hearing loss from our study population, we aimed to exclude participants with altered hearing thresholds due to conductive hearing loss or noise-induced hearing damage.

Rosen et al. were the first to investigate whether a change in diet affects hearing loss in older adults (40-60 y). They showed better hearing in subjects receiving a low-fat diet and worsening of hearing in subjects receiving a diet high in saturated fat (8). In contrast, we did not show significant differences between quartiles of saturated fatty acids. However, one has to keep in mind that plasma saturated fatty acids can not provide direct information on absolute saturated fat intake. Although plasma saturated fatty acids are dependent on their absolute concentrations and relative proportions in food, they also include endogenously synthesized saturated fatty acids (12).

Our analyses are the first to show an inverse relationship between plasma very long-chain n-3 PUFA proportions and age-related hearing loss in older adults. This study has several strengths, including a longitudinal design, the use of plasma proportions of very long-chain n-3 PUFA as a valid estimate of dietary intake of fatty acids (13) and sound audiometric assessments under standardized test conditions. Nevertheless, several issues should be addressed to enable a balanced interpretation of the findings.

First, plasma very long-chain n-3 PUFAs were associated with hearing loss in the low frequencies, but not significantly with hearing loss in the high frequencies. The apex of the cochlea transduces the low-frequencies sounds, whereas the base of the cochlea is responsible for the transduction of the high-frequencies sounds. Since the inner ear is an end organ and is only supplied by one or sometimes two arteries (14), microvascular disease could affect the blood supply to the

cochlea. As the apex of the cochlea is the farthest away from the blood supply, it may be most susceptible to changes in the microcirculation (15), and therefore particularly affect hearing thresholds on the low frequencies (3). An improvement in microcirculation may explain the association of plasma very long-chain n-3 PUFAs with low-frequency thresholds. Alternatively, more variation in the hearing threshold in the high frequencies compared with the low frequencies, may explain why we did not detect a significant difference between very long-chain n-3 PUFA quartiles and hearing thresholds on the high-frequencies with the current study sample size.

A second study-related issue that needs to be addressed is that half of our participants received folic acid supplementation for three years, because our study population originally participated in a randomized controlled trial. This folic acid treatment has been shown to slow down the decline in hearing in the low frequencies (9). Our stratified analyses show that

higher proportions of plasma very long-chain n-3 PUFA were still associated with less hearing loss in the low frequencies in the placebo group, but not in the folic acid group. Although the mean hearing thresholds in the folic acid group were not significantly different across the quartiles, the results were in the expected direction. This suggests that the treatment effect of folic acid overruled a potential association between plasma very long-chain n-3 PUFA and hearing loss in the folic acid group.

A third issue is the apparent inconsistency between the cross-sectional and the longitudinal results. Because our study population consisted of relatively young subjects (mean age: 60 yrs), it could well be that hearing disabilities are just beginning to develop in our participants. This corresponds with our findings that subjects with higher mean hearing thresholds at the start of the study also had a faster threshold increase than subjects with lower mean hearing thresholds at baseline.

Two other issues that require attention are the actual difference in hearing loss between the quartiles and the range of plasma very long-chain n-3 PUFAs. The difference in hearing loss between the highest and the lowest quartile of plasma very long-chain n-3 PUFAs appears to be small: -1.2 dB for the whole study population and -1.8 dB when only the placebo group was considered. However, since hearing loss increases over time and since our study population was relatively young, the difference between the quartiles could be greater in older populations. This is supported by our findings of a difference in hearing loss between the highest en lowest quartile of -0.8 dB in subjects of 50-60 yrs, and -1.5 dB in subjects of 60-70 yrs. Moreover, although the range of plasma very long-chain n-3 PUFA proportions in our study population was similar to that of other large studies in older adult populations (12, 16), it could be possible that the differences in hearing loss between the quartiles become even more pronounced if this range would have been wider.

Finally, it is important to realise that our study population may not represent a random sample of the Dutch older adult population, because our subjects were selected on the basis for participation in a randomized controlled trial (e.g. moderate levels of homocysteine, no vitamin B12 deficiency, no lipid-lowering drugs). This may affect the generalizability of our results.

In summary, these analyses provide us with encouraging results on an inverse association between very long-chain n-3 PUFAs and hearing loss. These results require confirmation from future observational studies to verify the direction, size and importance of the reported associations.

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